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Case report

# Temporal recruitment of cortical network involved in reading epilepsy with paroxysmal alexia: A combined EEG/MEG study

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## 1. Introduction

Reading epilepsy is a reflex epileptic syndrome in which all seizures are precipitated by the act of reading.[1] Seizures characteristically consists of reading-induced myoclonic jerks of the jaw or throat which may progress to secondary generalized tonic–clonic seizures if reading is not interrupted. In atypical forms many other types of ictal symptoms have been described[2]: abrupt loss of consciousness, absences, visual symptoms and paroxysmal alexia or dyslexia that suggests a left posterior cortex involvement.[3]

Reflex seizures are classified as electroclinical syndromes with no specific age relationship and can occur as occasional and caused events (alcohol withdrawal, fever), as part of an epileptic syndrome, or as reflex syndrome in which seizures are triggered only in response to a specific trigger, such as reading. The incidence and prevalence of reading epilepsy are unknown but it is probably under diagnosed.[1]

The anatomical basis of ictogenesis in reading epilepsy remains poorly understood. Combined EEG, MEG and functional magnetic resonance imaging (fMRI) studies have found left-dominant activations of motor and premotor cortical areas,[4,5] but only one MEG study[6] tackled the neuronal recruitment chronology. We performed a combined EEG/MEG study to highlight the spatio-temporal pattern of cortical network involved in the seizure of a patient affected by reading epilepsy.

## 2. Methods

The patient was a 31-year-old right-handed man. His medical history was marked by a single febrile seizure at the age of 2 during whooping cough and for a family history of epilepsy: the grandfather presented tonic–clonic seizures of unknown origin and his father had seizures suggesting a probable temporal focus.

The first epileptic episode occurred when he was 20-year-old in the night during reading: he suddenly experimented jaw and facial myoclonic jerks followed by a generalized tonic–clonic seizure with morsus. The next year during sleep deprivation for military service he had another similar attack. He reported that myoclonic jerks were more likely to occur when reading difficult material, small fonts, during late afternoon or evening, or when he was tired.

Previous EEG recordings were normal. The third seizure had occurred 10 years later after sleep deprivation when he was watching a film with Italian subtitles. This episode was characterized by head and eyes deviation to the left with a fencer posture of the arms followed by secondary generalization.

When he was admitted to our clinic, neurologic and MRI examinations were normal. Polygraphic video-EEG (1000 Hz sampling rate, filtered at 1–40 Hz for scalp EEG and 10–60 Hz for EMGs), recorded in the late afternoon following a period of partial sleep deprivation, showed that jaw myoclonic jerks of the bilateral masseter muscles were associated with bilateral fronto-temporal–parietal sharp-waves.

Patient gave their written informed consent according to the Declaration of Helsinki; the general procedures were approved by the local institutional ethics committee.

MEG and EEG were simultaneously recorded (1025 Hz sampling rate) using the neuromagnetic whole-head system equipped with 165 SQUID magnetometers and EEG channels placed on the scalp in standardized positions (Fp1, Fp2, F3, F4, F6, F7, C3, C4, P3, P4, FZ, CZ, PZ, T3, T4, T5, T6, O1, O2) according to the 10–20 system. Cardiac and ocular activities were also monitored by means of bipolar electrodes placed on the chest and on periorbital region to monitor possible heart and eyes contaminations of the MEG signals. Spontaneous activity recordings were performed with open and closed eyes (10 min each), during hyperventilation, photic stimulation and during reading silently a scientific paper in Italian language. MEG and EEG data were band-passed filtered at 1–40 Hz.

Volumetric anatomical image obtained using a Philips scanner at 1.5 T was transformed into Talairach space and coregistered to MEG coordinate system. An experienced neurophysiologist identified and marked the abnormal electrical activity on EEG channels. Corresponding MEG epochs without artifacts were

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averaged and used to localize the epileptic discharges. Then, for the averaged abnormal event, generators of the abnormal activity were identified on MRI image of the patient's brain: LORETA (low resolution topographic analysis) algorithm[6] implemented in BESA software was used to estimate for each millisecond the intensity of the abnormal activity at each voxel of the 3D volume grid of 7 mm which approximated the cortical surface of the patient. LORETA estimated the generators of abnormal activity providing activation maps for each millisecond, consisting of blurred images of point sources centered on the location of the maximal activity.[7]

The neurophysiologic and clinical data were compatible with the diagnosis of reading reflex syndrome. He was started on levetiracetam titrated to 2000 mg/day.

## 3. Results

Reading (both silently and aloud) in the late afternoon consistently evoked sharp and slow wave complexes over the right and left fronto-temporal–parietal regions at 0.5 Hz with maximal amplitude of about 200 uV over right frontal channels (Fig. 1A) which ceased when the patient stopped reading. Clinically, the patient presented myoclonus jaw jerks of the bilateral masseter muscles (Fig. 1A) occurring 30–35 ms after the onset of the epileptic discharges. He suddenly interrupted reading, looked up, and reported that he was feeling strange and unwell. He remained awake and presented paroxysmal alexia. Alexia appeared when patient interrupted reading after the reflex myoclonic seizure. During alexia, that lasted few seconds, EEG showed a postictal teta activity on bilateral fronto-temporal channels. At the end of the discharge MEG signals revealed the activation of the left parietal cortex with the highest activity strength (160 nAm/cm$^3$). The epileptic discharges appear first sporadically and then about one for second with the spike-wave complex morphology over the frontal derivations. Bilateral temporal channels showed muscular artefacts between the epileptic discharges due to the jaw jerks induced by reading.

Fig. 1, showing the single epileptic discharge and obtained combining EEG/MEG acquisitions (Fig. 1B–D), evidenced the bilateral frontal lobe involvement during reading. Sharp-waves were found over right and left frontal electrical channels (Fig. 1B) corresponding to fast (100 ms in duration) and high amplitude (±450 fT) waves over magnetic fronto-central channels. A similar cortical recruitment pattern was evident for the single and the averaged epileptic discharge showed during the entire recording session. LORETA results (Fig. 1D and Table 1) on epileptic discharge recorded by MEG identified a cortical network involving sources located in the left and right middle frontal gyrus (LMFG, RMFG), in the bilateral supplementary motor area (SMA), in the left motor cortex (LMC), in the bilateral primary sensory motor face area (PSMFA) and in the left inferior parietal sulcus (LIPS). Considering the activation of SMA and LMC as zero time, the spatiotemporal pattern of cerebral sources was characterized by an initial source (−28 ms) located in the bilateral MFG, followed by sources located in the SMA and LMC and by a source at 30 ms in the PSMFA. The maximum magnetic field power was characterized by a source in LIPS at 92 ms with the highest activity strength (160 nAm/cm$^3$). The frontal cortical sources showed a peak of activity also at 0 ms during the activations of SMA and LMC (Table 1).

## 4. Discussion

In this case of reflex reading epilepsy we found a right and left MFG hyperactivation in the early event with a bilateral to left and anterior to posterior cortical recruitment. We identified a precise spatiotemporal activation of specific brain sources: MFG, SMA and LMC, PSMFA and LIPS. Considering the role of SMA at seizure onset

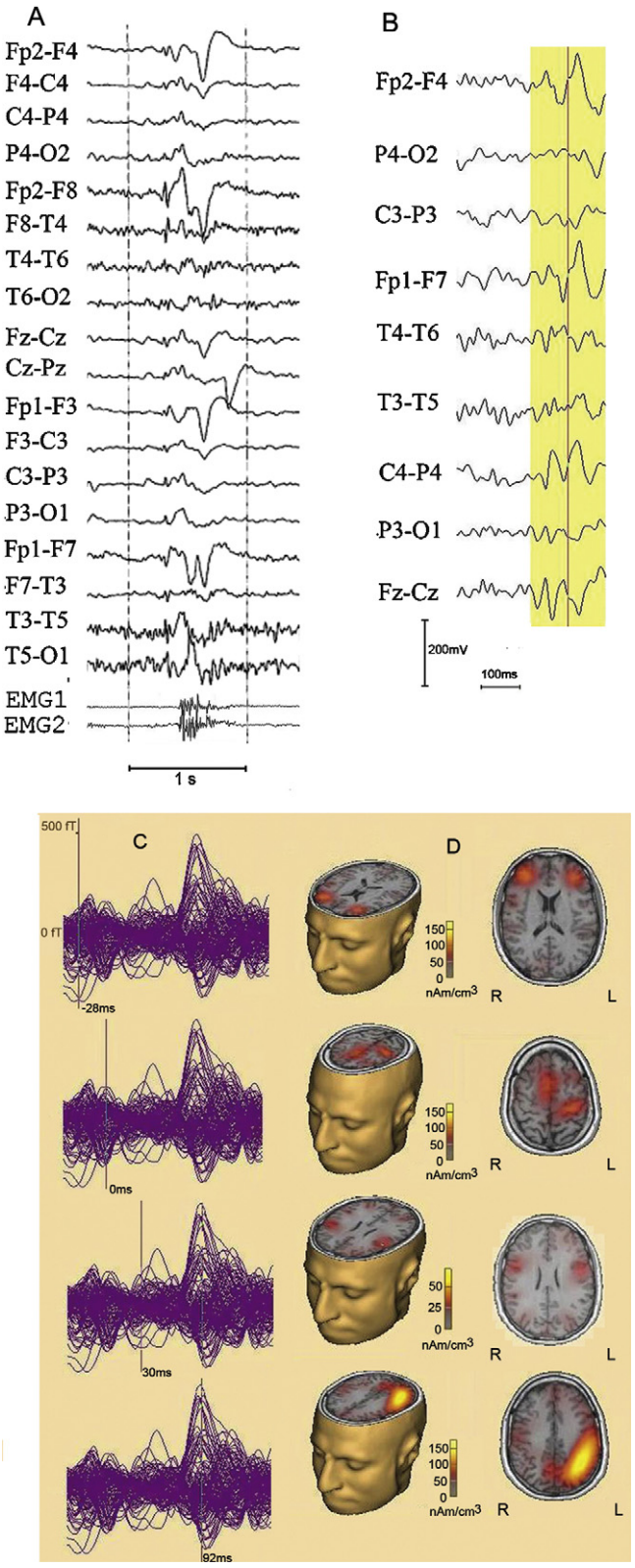


**Fig. 1.** (A) EEG epileptic discharge during silent reading performed in the late afternoon: single spike-wave complex over bilateral fronto-temporal derivations with maximal amplitude (200 μV) over right frontal channels. EMG1 and EMG2 record the left and right masseter myoclonus jerks respectively. (B) Selected EEG discharge during EEG/MEG simultaneous recording. The yellow bar highlights the temporal window selected for MEG localization during the sharp waves discharge. (C) Temporal pattern of all magnetic channels related to the discharge. (D) Neuronal recruitment chronology within the identified network: localization of MEG activity by means of LORETA at different temporal instants (−28, 0, 31 and 92 ms): we considered at 0 time the activation of the supplementary motor area.

**Table 1**
Talairach coordinates, temporal sequences and strength of brain sources activated during abnormal magnetic activities induced by the reflex seizure.

| Brain areas | Talairach coordinate (mm) | Activation peak (ms) | Intensity peak (nAm/cm$^3$) |
|---|---|---|---|
| LMFG | 33; 40; 14 | −28; 0 | 80; 62 |
| RMFG | −37; 39; 14 | −28; 0 | 98; 75 |
| SMA | 8; 2; 56 | 0 | 78 |
| LPC | −30; −30; 52 | 0 | 83 |
| LPSMFA | −47; 5; 27 | 30 | 36 |
| RPSMFA | 44; 10; 27 | 30 | 31 |
| LIPS | −40; −44; 38 | 92 | 160 |

LMFG: left middle frontal gyrus, RMFG: right middle frontal gyrus, SMA: supplementary motor area, LMC: left motor cortex, LPSMFA: left primary sensory motor face area, RPSMFA: right primary sensory motor face area, LIPS: left inferior parietal sulcus.

in similar cases[5,8] with right perioral myoclonus jerks characterized by left SMA and left PSMFA activation, we suggested that the bilateral MFG could represent the trigger zone; whereas the SMA and the LMC represent the epileptogenic zone. The motor face areas activation could represent the symptomatogenic zone related to myoclonus jerks. The recruitment of the left parietal cortex could be responsible for the paroxysmal alexia referred by patient.[3] The role of MFG, SMA, motor and parietal areas in language and in reading supports our hypothesis[4,5,8–10] of a network that expands over different brain areas with specific temporal recruitment.

Indeed reading-induced seizures could arise from areas of cortical hyperexicitability which overlap with regions normally involved in reading, a complex cognitive process characterized by visual analysis, memory functions, conversion of written words to phonetic language and articulation and acoustic monitoring. Grapheme to phoneme transformation appears to be the critical stimulus in reading reflex seizures: if some authors[11] evidenced that lexical and non-lexical stimuli induced seizures showing increased discharge rates when the patient was reading aloud or silently articulating, others[12] showed that seizures were most readily elicited when the patient read aloud. In the study of Vercelletto and colleagues[13] only one of 11 patients had seizures exclusively in reading aloud. We thought that the higher integrating systems of language are essential in inducing reading reflex seizures: we support the putative role of dominant premotor cortex in activation of precise sequences of motor linguistic output and the anatomic relevance to the phonologic component of reading. The involved cerebral structures can represent a possible "reading network" (the modern concept of system-epilepsy) that can be perturbed by the presence of an "epileptic reflex focus". Our findings confirmed recent combined EEG-fMRI and MEG studies[8,14] evidencing that the dominant motor and premotor cortex as well as the supplementary motor area represent the primary sources of the epileptic activity in reading epilepsy.

We confirmed previous studies[4] also suggesting that the early activation pattern related to the abnormal neuronal activity was located in the MFG and followed by the recruitment of SMA and motor and parietal areas.

Yet the different onset of the seizure can induce different symptoms in reading epilepsy due to the involvement of occipital or temporo-occipital,[15] temporal,[1] parietal or temporo-parietal,[16] or frontal[4] areas.

We suggest that the reason for these discrepancies is dependent on possible recruitment of each cerebral area of the "system of reading". We hypothesize that the high intensity activation of the left parietal component of the reading network induces alexia. A recent article 15 corroborates our hypothesis showing a posterior contribution of the dominant cerebral cortex in a variant of reading epilepsy with partial seizures manifested by visual symptoms and a- or dyslexia. These seizures originate from the posterior region of the dominant hemisphere, corresponding to the posterior part of the neural network that underlies the function of reading. In conclusion our study suggests that the presence of the epileptic focus in specific cerebral networks[17–19] could also produce an hyperactive neuronal circuit causing a reflex seizure.

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